Rule 126 --30. A pharmaceutical composition comprising an effective anesthetic amount of the compound according to claim 23 and a pharmaceutically acceptable carrier.--

--31. A method of treatment which ~~comprises~~ administering to a patient in need thereof an effective anesthetic amount of the composition of claim 30.

REMARKS

Election/Restriction

The Examiner requests restriction to one of the following inventions: Group I – claims 1-5, 8-12 and 16-18; Group II – claims 1-5, 8-12 and 16-18; Group III – claims 6, 7 and 13-15. The Examiner contends that these are different inventions since "there is no common core present which is essential to the utility". The applicants respectfully traverse. 35 U.S.C. § 121 only provides authority for restriction between claims. As can be seen from the listing above, Group I and Group II are not directed towards different claims, indicating that at least one generic claim is present. In the present case, claims 1, 8 and 16 are generic with various dependent species claims. 37CFR 1.141(a) states that a reasonable number of species may be claimed in a single application provided that a generic claim is included and all species claims are written in dependent form. It appears that the Examiner has focused on the differences in the R – O group to conclude that Group I has no "common core present which is essential to the utility". This is untrue. All of the species are prodrug moieties. More specifically, the common core of these species is the phosphonooxymethyl prodrug moiety, $-O(CH_2)_nOPO(OR_1)(OR_2)$, which is essential for their utility, i.e. their increase in aqueous solubility and ability to quickly break down *in vivo*. So in the present case, while the claims cover a number of species, the species do have a common structure and applicants are entitled to obtain examination of their generic claim. The number of species encompassed by the generic claim is no basis for a restriction requirement. As stated in *In re Weber* (580 F.2d 455, 458):

> " It is elementary patent law that the number of 'species' 'covered' by a patent having a generic claim is virtually without limit notwithstanding the limitation of Rule 141 to five species 'specifically claimed.' So the discretionary power to limit one application to one invention is no excuse at all for refusing to examine a broad generic claim – no

matter how broad, which means no matter how many independently patentable inventions may fall within it."

Hence, a species election requirement is more appropriate, not a restriction requirement. The applicants elect Propofol as a species with traverse. However, if the Examiner maintains the request for a restriction, the Applicants elect with traverse Group I; claims 1-5, 8-12 and 16-18 where the R-O group represents Propofol.

Rejections Under 35 USC § 112

The Examiner has rejected claim 16 as being indefinite and failing to point out the subject matter of the invention. Specifically, the Examiner requests utility for the compound recited in claim 16. The applicants respectfully traverse. Claim 16 has been amended to better clarify the utility. However, since this is a generic claim, no species-specific utility is included. Claims 19- 21 have been added to better describe the species-specific utility that the generic claim provides.

Rejections Under 35 USC § 102

The Examiner has rejected claims 1 and 3 as being anticipated by Cho in addition to Varia. With respect to Cho, the Examiner contends that the metronidazole phosphate dipotassium salt in scheme I on page 412 anticipates the instant claims. The applicants respectfully traverse. A close inspection indicates that the compound cited in Cho does not contain the additional $(–O–)_n$ linkage (where "n" is an integer between 1 and 2, see claim 1) present in the current invention. In other words, the Cho compound is a direct phosphate ester while the compounds of the present invention are indirect phosphate esters.

In the Varia publication, the Examiner asserts that the compounds of formula IV, page 1087 anticipates the current invention (here, R = $–PO_3^{2-}Na_2^+$). The applicants traverse. Here, again, the compound cited in Varia does not contain the additional $(–O–)_n$ linkage (where "n" is

an integer between 1 and 2, see claim 1) present in the current invention. That is, the Varia compound is a direct phosphate ester, not the indirect phosphate ester of the current invention.

Rejections Under 35 USC § 103

The Examiner has rejected claims 1-5, 8-12 and 16-18 for obviousness, citing Jones in view of Bundgaard. However, a combination of Jones and Bundgaard does not even establish a prima facie case of obviousness. The Jones publication discloses pharmaceutical compositions of Propofol for producing anesthesia, but does not teach prodrugs. The Bundgaard publication teaches that direct phosphate esters are commonly used for increasing water solubility. The Examiner contends that one skilled in the art would be motivated to use the phosphate ester method taught by Bundgaard on the alcohol containing drug (Propofol) taught by Jones to achieve the current invention. The applicants respectfully traverse. Bundgaard teaches modification of a poorly soluble drug to a **direct** phosphate ester. This method does not produce the current invention, nor does it suggest the type of modification disclosed by the current invention, which is an **indirect** phosphate ester.

Even if a prima facie case of obviousness was established, this would still be rebutted by the unexpected results of the present invention. Applicants have performed experiments directly comparing the propofol prodrug of the present invention (indirect phosphate ester) with the corresponding direct ester and have shown that a direct phosphate ester **does not** have anesthetic effect, as detailed in the accompanying Declaration by Dr. Roger Rajewski. In this Declaration, the results of *in vitro* and *in vivo* comparisons are presented for two Propofol compounds, one being a direct phosphate ester, Phosphopropofol, (which is all that could be taught by a combination of Jones and Bundgaard) and the other an indirect phosphate ester (O-phosphonooxymethylpropofol) as taught by the current invention. The results clearly indicate that the prodrug from the current invention is superior to that produced using the direct phosphate ester method, as evidenced by the lack of anaesthetic effect for the direct phosphate ester at nearly twice the HD50 dose of the indirect phosphate ester.

Accordingly, in view of the above amendments and remarks, reconsideration of the rejections and allowance of the claims of the present application are respectfully requested.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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